Literature Review:
IOVS and J Neuroscience

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PhNR in LHON

The Photopic Negative Response: An Objective Measure of Retinal Ganglion Cell Function in Patients With Leber’s Hereditary Optic Neuropathy

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LHON

- 1\textsuperscript{st} human disease associated with mtDNA point mutation (Wallace D, et al, 1988)
- 3 primary pathogenic mutations (11778, 14484, 3460)
- Predictable clinical phenotype
- Mutation causes reduced Complex I activity
- “Built in” window of intervention:
  - Second eye involvement in 97\% of patients within 1 year after 1\textsuperscript{st} eye
Treatment of LHON: General Challenges

- Rarity
- Spontaneous recovery (mutation, age of onset)
- Relatively narrow window of opportunity to intervene
- Difficulty with functional metrics: visual acuity, visual field, contrast sensitivity
Photopic negative response (PhNR)

- Originally described by Viswanathan et al (IOVS, 1999)
- Arises from ganglion cell layer; attenuated with experimentally induced RGC death
- Provides objective data regarding RGC function
- Functional changes precede structural changes
Design

- 6 symptomatic LHON patients, 6 asymptomatic carriers, and 6 controls
- All patients and controls had 11778 mutation
- Standard eye exam, ETDRS, perimetry, and OCT
- All underwent photopic ERG with PhNR measurements
  - PhNR performed using red stimulus on blue background
  - Automated detection of PhNR amplitude with manual removal of movement artifact
• PhNR reduced in patients compared with controls
• PhNR also reduced in carriers compared with controls
• Small correlation between PhNR amplitude and OCT
Conclusion

- PhNR may be a potential marker of RGC function in LHON
- Could be used in clinical trials to monitor visual function and correlate with structural changes
- Questionable value for routine clinical purposes
- Variability in PhNR techniques and reproducibility may be a challenge
- Potential prognostic role in asymptomatic carriers
OCT Angiography in Migraine

Foveal and Peripapillary Vascular Decrement in Migraine With Aura Demonstrated by Optical Coherence Tomography Angiography

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Migraine and Stroke

- Migraine with visual aura is a risk factor for ischemic stroke
- Migraine with VA also associated with increased risk of ocular ischemic events (NAION, RAO)
- Mechanism underlying increased risk of ischemia unclear
- Previous studies have shown conflicting results regarding retinal vascular changes in migraineurs (Rose et al)
- OCT angiography relatively novel method of assessing retinal and optic nerve microvasculature and perfusion in vivo
Design

- 3 groups of subjects:
  - Migraine with visual aura
  - Migraine without visual aura
  - Normal controls
- All groups characterized by International
- All subjects matched for age and standard OCT exclusion criteria (refractive error, known optic nerve or retinal pathology)
- All subjects underwent standard OCT of optic disc and macula, as well as OCT angiography disc & macula
Foveal avascular zone larger in migraine with visual aura subjects
• Larger FAZ in MA subjects
• Decreased foveal vessel density in MA subjects
• Decreased peripapillary vessel density in MA subjects but only superiorly
Conclusions

- Microvascular changes are present in patients having migraine with visual aura.
- These microvascular changes could be related to the increased risk of ischemic events in patients with migraine and visual aura.
- The exact mechanism remains uncertain.
- No longitudinal follow up.
- OCT-A metrics still being developed and standardized.
Omega 3 Polyunsaturated Fatty Acids as a potential treatment for NAION

Neuroprotective Effects of Omega-3 Polyunsaturated Fatty Acids in a Rat Model of Anterior Ischemic Optic Neuropathy

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NAION and Treatment

- No proven treatment for NAION
- Impaired perfusion of optic nerve head, with subsequent ischemic injury
- Neurogenic inflammation may play a role in neural injury in NAION (Salgado C et al, Arch Ophthalmol 2011)
- Rodent model of NAION can be used to study potential treatment strategies
Omega 3 Polyunsaturated Fatty Acids - Rationale

- O3 PUFAs may transition pro-inflammatory macrophages to anti-inflammatory
- Also stabilize damaged blood-brain barrier after ischemic injury
- Potential to limit neuronal and axonal injury in NAION
Design

- Rodent model of NAION
- Outcomes included:
  - RGC density
  - Flash VEP
  - Arachidonic acid/eicosapentaenoic acid levels (high levels surrogate for pro-inflammatory cytokines)
- 6 in each group
  - Treated group: received PUFAs 3 days prior to induction of NAION, with continued administrated for 6 days
  - Control group
Results:

• Increased density of RGCs in treated group

• Reduced # of apoptotic cells in treated group

• Reduced # of pro-inflammatory cytokines (AA/EPA levels) in treated group

• F-VEP latencies similar
Conclusions

- Omega 3 PUFAs may be a potential treatment for human NAION
- Need further studies, both in animal and human models
- Functional outcome (F-VEP) similar, so not clear if there is a clinically relevant effect
Driving safety in the elderly using monitored driving data

Visual Sensory and Visual-Cognitive Function and Rate of Crash and Near-Crash Involvement Among Older Drivers Using Naturalistic Driving Data

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Purpose. An innovative methodology using naturalistic driving data was used to examine the
Driving safety has enormous implications: cost, health care resource allocation, etc

Prior studies regarding driver safety have relied upon self-report and crash data (police reports)

These methods may distort or misrepresent driver safety and relationship to visual function
Design

- 659 elderly (>70 years) drivers recruited for study
- Vehicles equipped with driver monitoring software
- All participants completed surveys
- All participants underwent comprehensive assessment of vision:
  - High contrast VA (logMAR)
  - Pelli-Robson contrast sensitivity
  - Perimetry
  - Clock drawing test (cognitive function and visual spatial performance)
  - Validated Driver Health Inventory (visual processing speed and useful field of vision)
- Main outcomes were crash and near-crash events
3 year driving period:

- ~25% with crash event
- 251 crashes/100,000 miles driven

**Visual acuity NOT related to crash events**

**Impaired contrast sensitivity in WORSE eye assoc/w crash events**

**Useful field of vision (visual processing speed) related to crash events**

**Impaired far peripheral visual field increased risk of crash**

### Table 2. Number and Rates of Crash, Major Crash, At-Fault Crash, and Near-Crash Involvement During the SIARP2 Study (N = 659)

<table>
<thead>
<tr>
<th>No. of Older Drivers</th>
<th>No. of Events</th>
<th>Rate per 100,000 Person Miles*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crash</td>
<td>166</td>
<td>251</td>
</tr>
<tr>
<td>Major crash</td>
<td>110</td>
<td>134</td>
</tr>
<tr>
<td>At-Fault crash</td>
<td>143</td>
<td>217</td>
</tr>
<tr>
<td>Near-crash</td>
<td>154</td>
<td>248</td>
</tr>
</tbody>
</table>

### Table 3. Continued

<table>
<thead>
<tr>
<th>Crash Involvement</th>
<th>Major Crash Involvement</th>
<th>At-Fault Crash Involvement</th>
<th>Near-Crash Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude RR (95% CI)</td>
<td>Adjusted RR* (95% CI)</td>
<td>Adjusted RR* (95% CI)</td>
<td>Adjusted RR* (95% CI)</td>
</tr>
<tr>
<td>P Value †</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥8</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>&lt;8</td>
<td>0.92</td>
<td>0.99</td>
<td>0.99</td>
</tr>
</tbody>
</table>

* Adjusted for age group (70–74, 75–79, 80–84, 85–89, 90+ years), sex, race, education, number of medical conditions, rapid walk status, cognitive impairment status, sensation-seeking score, and prior MVC involvement.
† P value obtained from the adjusted model.
§ Contrast sensitivity impairment based on better eye, assigning a 0.78 sensitivity to those who could not see anything.
∥ Contrast sensitivity impairment based on worse eye, assigning a 0.78 sensitivity to those who could not see anything.
• Field loss at 70' or 85' temporally in either eye.
★ Field loss at 70' or 85' temporally in both eyes.
Conclusions

- Relationship between visual function and driver safety is complex and multi-dimensional
- Contrast sensitivity and visual processing may play a major role in driver safety
- “Naturalistic” driver data studies are feasible
- Software metrics may not have detected all crash events
- Mostly Caucasian population, so unclear whether this generalizes to other ethnic groups
Cortical spread depression results in changes in the glymphatic system.
Glymphatic system

- Pathway that regulates CSF egress through paravascular spaces
- Involved in the clearance of extracellular macromolecules
- Main function may be removal of neurotoxic waste products from brain into paravascular compartments
- Aquaporin 4 channels present on astrocytic endfeet in paravascular spaces
Cortical Spread Depression

- Substrate of migraine visual aura
- Wave of neuronal excitation and depression
- Involves inflammatory cascade which includes NO and COX-2
- Vascular changes correlate with neuronal activity
Is there a relationship between CSD and the glymphatic system?

- Investigators performed transcranial imaging using 2 photon microscopy in rodents
- Utilized validated rodent model of CSD (craniotomy and pinprick)
- CSF was labelled and tracked, to quantify clearance
- Study group (induced CSD) and control group
- Induction of CSD was followed by rapid closure of surface paravascular spaces.
- Penetrating arteries likely affected but could not be fully assessed.
- Impaired clearance of CSF in CSD mice.
Conclusions

- CSD results in structural and functional changes in glymphatic system
- Impaired clearance of CSF could result in build up of neurotoxic waste products
- May be clue to link between migraine with visual aura and cerebral ischemia
- Unclear whether this is generalized to humans and spontaneous CSD
- Relationship to future ischemic events speculative